REMARKS

In general, applicants' invention features a novel gene family, the members of which encode regulators that control the onset of acquired resistance responses. The invention is based, in part, on applicants' discovery of a gene encoding a novel protein containing ankyrin repeats, as well as their finding that the transformation of the cloned gene into plants confers broad-spectrum disease resistance. Importantly, the invention provides for the genetic engineering of long-lasting, broad-spectrum resistance in crops.

The Office Action

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected, under 35 U.S.C. § 112, first paragraph. Claims 1, 2, 4-13, 15-29, 36, and 40-42 also stand rejected under 35 U.S.C. § 112, second paragraph. In addition, the specification was considered informal in the arrangement of the subheadings. Each of these rejections is addressed as follows.

Specification

The Examiner has indicated that the application is informal in its arrangement, and has requested that the subtitle referring to the "Detailed Description of the Invention" be repositioned in the specification. By the present amendment, applicants have complied with this request.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the disclosure in applicants' specification (1) fails to provide a written description of the claimed invention and (2) is not commensurate in scope with the claimed invention. For the following reasons, each of these rejections is respectfully traversed.

Written Description

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected, under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. Applicants respectfully traverse this basis of the rejection.

The adequate written description requirement of 35 U.S.C. § 112, ¶ 1 provides that

> the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...

The written description requirement serves "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). In order to meet the written description requirement, the applicant need not utilize any particular form of

disclosure to describe the subject matter claimed, but "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Stated another way, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991).

The claims in question are generally directed to products and methods that include the inventors' novel gene family encoding ankyrin-repeat-containing polypeptides that, when expressed in a plant, confer disease resistance. Independent claim 1, for example, reads:

> 1. An isolated nucleic acid molecule encoding an acquired resistance polypeptide comprising an ankyrin repeat, wherein said acquired resistance polypeptide confers, on a plant expressing said polypeptide, resistance to a plant pathogen.

And independent claims 10, 11, and 12 read:

> 10. An isolated nucleic acid molecule that specifically hybridizes to a nucleic acid molecule comprising the genomic nucleic acid sequence of Fig. 4 (SEQ ID NO:1), wherein said isolated nucleic acid molecule encodes an acquired resistance polypeptide comprising an ankyrin repeat that confers, on a plant expressing said polypeptide, resistance to a plant pathogen.

11. An isolated nucleic acid molecule that specifically hybridizes to a nucleic acid molecule comprising the cDNA of Fig. 5 (SEQ ID NO:2), wherein said isolated nucleic acid molecule encodes an acquired resistance polypeptide comprising an ankyrin repeat that confers, on a plant expressing said polypeptide, resistance to a plant pathogen.

12. An isolated nucleic acid molecule that specifically hybridizes to a nucleic acid molecule comprising the DNA sequence of Fig. 7A (SEQ ID NO:13), wherein said isolated nucleic acid molecule encodes an acquired resistance polypeptide comprising an ankyrin repeat that confers, on a plant expressing said polypeptide, resistance to a plant pathogen.

Applicants' specification clearly describes to the skilled worker what is claimed. The specification, for example, at page 43 (line 27) - page 44 (line 13), teaches the ankyrin repeat consensus that is found in polypeptides encoded by the claimed gene family. And Figures 6A and 6B depict the region identified by applicants as the ankyrin-repeat consensus. Clearly, based on this description, one skilled in the art would recognize that applicants' invention encompassed—not one gene—but a family of genes encoding ankyrin-repeat-containing, disease resistance polypeptides, and, on this basis alone, the rejection may be withdrawn.

Moreover, applicants wish to address two specific points raised in the Office Action. First, contrary to the assertion that the ankyrin motif includes merely a small region of the disclosed molecule, applicants note that, in fact, the repeat consensus spans over at least 20% of the encoded gene product, from about amino acid 265 to about amino

acid 393. The ankyrin motif is therefore not an insignificant feature of the disease-resistance-conferring protein. Rather, as is discussed above, the ankyrin consensus sequence provides a diagnostic feature that is readily recognizable to the skilled worker.

Second, and again contrary to the assertions in the Office Action, applicants' ankyrin repeat-containing protein family does indeed exist and its members can indeed be distinguished from unrelated genes containing this motif. As is readily appreciated by the Office, applicants' ankyrin-repeat-containing protein confers, on a plant expressing such a protein, disease resistance. As a result of this feature, the polypeptide is readily distinguishable from other ankyrin-repeat-containing polypeptides that have been described in the literature, which, to the best of applicants' knowledge, have not been shown to possess this property. Moreover, because acquired resistance plant defense responses are ubiquitous in the plant kingdom, and because applicants have demonstrated that an ankyrin-repeat-containing polypeptide controls the onset of such responses in *Arabidopsis*, it is entirely reasonable to assume that other plants possess and express such genes to regulate disease resistance. The Office's concerns that applicants' claimed family of nucleic acid molecules does not exist or that its members could not be identified are therefore unwarranted.

In sum, there can be no question that applicants were in possession of the claimed genus at the time their application was filed, and that one skilled in the art would recognize applicants' disclosure as a description of the invention defined by the present

claims. As a result, applicants' specification clearly satisfies the written description requirement, as set forth by the case law, and applicants request reconsideration and withdrawal of this basis for the § 112 rejection.

Scope of Enablement

Claims 1, 2, 4-13, 15-29, 36, and 40-42 also stand rejected under § 112, first paragraph based on the assertion that the teaching of applicants' specification is not commensurate in scope with the present claims. The rejection essentially turns on the assertion that it would require undue trial and error experimentation to identify genes which are structurally and functionally related to the disclosed isolated nucleic acid molecule that encodes the polypeptide of SEQ ID NO: 14. This rejection should be withdrawn.

Applicants submit that the specification clearly enables the subject matter presently claimed. In particular, given the teaching of the specification and the level of skill known in the art at the time the present application was filed, applicants submit that genes falling within the scope of applicants' claims not only existed throughout the plant kingdom, but could be routinely identified and isolated from a variety of sources using standard techniques of molecular biology.

On gene isolation methodologies, applicants again point out that clear instructions for isolating the claimed nucleic acid molecules are provided in their specification, under the heading "Isolation of Solanaceous AR Genes," at pages 49-50, and also under the

heading "Isolation of Other Acquired Resistance Genes," at pages 50-52. There, applicants provide general guidance on the routine methods known at the time the application was filed for identifying the gene sequences required by the claims. These standard cloning methods described in the specification include: (1) the design and utilization of oligonucleotides for cloning acquired resistance gene sequences, (2) low- and high-stringency hybridization cloning methodologies, (3) library screening procedures, and (4) PCR-based amplification cloning strategies. Using such techniques, AR genes may be readily isolated from virtually any plant using applicants' *NPR1* sequence as a starting material.

In addition, once isolated, these gene sequences may be subjected to standard DNA sequencing to confirm their structural relatedness to the disclosed *NPR1* gene and its encoded ankyrin-repeat-containing polypeptide. If desired, publicly available sequence analysis software may be utilized for rapidly identifying the ankyrin-repeats. It cannot be disputed that all of the above methods are routinely used in the art of molecular biology and that all were well established at the time applicants filed their application.

In addition, as further evidence that genes encoding applicants' ankyrin repeat-containing, disease resistance polypeptides may be isolated using nothing more than standard techniques, the Examiner is directed to the present specification, for example, at pages 49-50. There, applicants demonstrate the successful and straightforward isolation of an *NPR1* homolog from tobacco. This homolog was identified by screening a cDNA

library with probe prepared from the full-length *Arabidopsis NPR1* cDNA. The isolated solanaceous acquired resistance gene, like the cruciferous *NPR1* gene, was found to encode an ankyrin-containing polypeptide. In addition, the tobacco NPR1 homolog shows significant sequence identity to the *Arabidopsis* NPR1 gene product. Consistent with these results in tobacco, applicants also direct the Office's attention to the present specification at page 52 (lines 4-15). There, results of an RNA blot experiment are described that demonstrate the existence of yet another *NPR1*-hybridizing RNA, in this case, in potato.

Such data strongly corroborate applicants' assertion that structurally related gene sequences falling within applicants' claimed invention exist, and that they may be identified and isolated from a variety of plant sources using standard techniques that are both described in the present specification and known in the art. There can be no question that the guidelines provided by the teachings of applicants' disclosure have been effective for such gene identification from at least two plants other than *Arabidopsis*, and there is no reason to believe that *NPR1* homologs cannot similarly be identified from any number of other sources. Accordingly, this ground for the enablement rejection, based on the alleged inability of a skilled worker to identify structurally related genes, should be withdrawn.

With respect to the issue of whether such genes would confer disease resistance, applicants again direct the Examiner to the present specification. As taught, for example,

at page 69 (lines 15-17), the ability of a structurally related gene to confer plant disease resistance is easily established using any of a variety of methods, including a straightforward, one-step screening technique. The specification makes clear that broad-spectrum pathogen resistance is readily obtained by expressing acquired resistance transgenes at sufficiently high levels to initiate a plant defense response. Moreover, at pages 45-46, the specification demonstrates that overexpression of a *35S-NPR1* transgene in *Arabidopsis* conferred resistance on the plant to bacterial and fungal pathogens. Accordingly, a skilled worker need only prepare transgenic plants overexpressing a gene found to be structurally related to *NPR1*, and then evaluate the plant's ability to combat a pathogen. Such a single-step screening approach cannot constitute undue trial and error experimentation. This basis of the enablement rejection should also be withdrawn.

In conclusion, applicants submit that the specification adequately describes the methods to be used to practice the invention, commensurate with the scope of the pending claims. Applicants know of no information a practitioner would require to carry out the invention that is not spelled out in detail in the application, or that was not known in the art when the application was filed. Accordingly, applicants respectfully request that the Office reconsider and withdraw the rejection under § 112, first paragraph.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected under 35 U.S.C. § 112,

second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 1, 10-12, and 36 were deemed indefinite in reciting the phrase "acquired resistance polypeptide." This rejection has been met by amending claims 10-12, along the lines of claim 1, as suggested by the Examiner, to indicate that the polypeptide functions to confer resistance to a pathogen.

Claim 4 was deemed indefinite in reciting "derived from." This rejection is respectfully traversed. Applicants point out that the meaning of this phrase is made clear by applicants' specification. For example, at page 11 (lines 17-19), the specification states:

> By "derived from" is meant isolated from or having the sequence of a naturally-occurring sequence (e.g., a cDNA, genomic DNA ...).

In view of this definition, it is requested that this basis of the § 112, second paragraph, rejection be withdrawn.

Claims 10-12 were deemed indefinite in reciting the phrase "specifically hybridizes to." The Office Action states:

> "[S]pecifically" is a relative term dependent on hybridization conditions. If Applicant intends a nucleic acid molecule which hybridizes to the NPR1 nucleic acid molecule and not to any other nucleic acid molecule, then such a limitation is dependent on the conditions under which the hybridization occurs, conditions which have not been defined in the claim or in the specification.

This rejection is respectfully traversed.

Applicants point out that the meaning of "specifically hybridizes" is made clear by applicants' specification. At page 12 (lines 1-3), the specification states:

> By "specifically hybridizes" is meant that a nucleic acid sequence is capable of hybridizing to a DNA sequence under at least low stringency conditions as described herein, and preferably under high stringency conditions, also as described herein."

Furthermore, contrary to the Office's assertion, applicants' specification, at pages 51 (line 12) - 52 (line 3), describes exemplary low and high stringency hybridization conditions. For example, with respect to exemplary high stringency conditions, the specification, at page 51 (lines 12-21) states:

> In one particular example of this approach, related AR sequences having greater than 80% identity are detected or isolated using high stringency conditions. High stringency conditions may include hybridization at about 42 °C and about 50% formamide, 0.1 mg/mL sheared salmon sperm DNA, 1% SDS, 2X SSC, 10% Dextran sulfate, a first wash at about 65 °C, about 2X SSC, and 1% SDS, followed by a second wash at about 65 °C and about 0.1X SSC. Alternatively, high stringency conditions may include hybridization at about 42 °C and about 50% formamide, 0.1 mg/mL sheared salmon sperm DNA, 0.5% SDS, 5X SSPE, 1X Denhardt's, followed by two washes at room temperature and 2X SSC, 0.1% SDS, and two washes at between 55-60 °C and 0.2X SSC, 0.1% SDS.

And, with respect to low stringency conditions, the specification, at pages 51 (line 22) - 52 (line 2), states:

> In another approach, low stringency hybridization conditions for detecting AR genes having about 40% or greater sequence identity to the AR genes described herein include, for example, hybridization at about 42°C and 0.1 mg/mL sheared salmon sperm DNA, 1% SDS, 2X SSC, and 10% Dextran sulfate (in the absence of formamide), and a wash at about 37°C and 6X SSC, about 1% SDS. Alternatively, the low stringency hybridization may be carried out at about 42°C and 40% formamide, 0.1 mg/mL sheared salmon sperm DNA, 0.5% SDS, 5X SSPE, 1X Denhardt's, followed by two washes at room temperature and 2X SSC, 0.1% SDS and two washes at room temperature and 0.5X SSC, 0.1% SDS.

Moreover, applicants' specification, at page 49 (lines 14-20), describes the following additional low stringency hybridization conditions:

> Hybridization was performed at 37°C in 40% formamide, 5X SSC, 5X Denhardt, 1% SDS, and 10% dextran sulfate. The filters were washed in 2X SSC for fifteen minutes at room temperature and 2X SSC, 1% SDS for thirty minutes at 37°C.

Given applicants' definition of the phrase "specifically hybridizes," and in view of the exemplary standard hybridization conditions set forth in applicants' specification, a skilled worker would have no trouble understanding the meaning of this phrase. Reconsideration on this issue is respectfully requested.

Claim 13 was deemed indefinite in reciting the term "mediates." This rejection has been met by the present amendment to claim 13 in which this term has been replaced with the term "activates."

Finally, claims 36 and 40 were deemed indefinite in reciting the phrase "positioned for expression." This rejection has been met by the present amendment to claims 36 and

40 in which the phrases "positioned for expression in the cell" and "wherein said nucleic acid molecule is positioned for expression in the plant cell" have been deleted. These phrases are unnecessary for properly interpreting each claim given that paragraph (b) of claim 36 requires culturing the "transformed cell to express the nucleic acid molecule or the vector," and paragraph (b) of claim 40 requires that "the nucleic acid molecule or vector is expressed in the transgenic plant."

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is respectfully requested. Enclosed is a petition to extend the period for replying for three months, to and including January 26, 2000. Also enclosed is a Notice of Appeal, in which applicants respectfully appeal the final rejection of the pending claims.

If there are any charges or credits, please apply them to deposit account number 03-2095.

Respectfully submitted,

Date: 1/26/00

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